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(54) Title: POROUS POLYMER MATERIAL AND METHOD OF PRODUCTION THEREOF

(57) Abstract: According to the present invention, there is provided a porous polymer material and a method of production thereof, where a large majority, for example 80 % or more, or even up to about 100 % of the material is in the form of substantially spherical beads with narrow bead size distributions. These polymeric beads have a porous structure, characterized by cavities joined by interconnecting pores (a HIPE structure), some of which are connected to the surface of the bead.

- 1 -

DESCRIPTIONPOROUS POLYMER MATERIAL AND METHOD OF PRODUCTION THEREOF

Crosslinked porous polymeric materials have been used for a variety of applications and have proved especially useful to the biomedical field, being used as label or sensing-device carriers. Other uses include affinity chromatography, immobilisation of enzymes, drug delivery and solid-phase synthesis of proteins.

U.S. Pat. No. 4,522,953, discloses crosslinked porous polymeric materials produced by polymerization of water-in-oil (W/O) high internal phase emulsions (HIPEs) where the ratio of oil to water is typically greater than 70% (P. Hainey, *et al.*, *Macromolecules* 1991, 24, 117; N. R. Cameron, *et al.*, *Adv. Polym. Sci.* 1996, 126, 163; A. Barbetta, *et al.*, *Chem. Commun.* 2000, 221). The HIPEs comprise a combination of a substantially water-insoluble monomer and a substantially water-insoluble crosslinker as the continuous phase (*e.g.*, styrene/divinylbenzene) and an aqueous discontinuous phase. Polymerization of the HIPE, usually by thermal free-radical initiation, followed by removal of the discontinuous phase leads to a porous material that is a replica of the original emulsion. The disclosed polymers have rigid porous structures characterized by cavities that are interconnected by pores in the cavity walls. The disclosed materials were hydrophobic but could be made hydrophilic by suitable surface functionalization as discussed in U.S. Pat. Nos. 4,536,521; 4,611,014 and 4,612,334.

The original process for synthesizing HIPE polymers produced monolith blocks of material that conformed to the dimensions of the reaction vessel (*i.e.*, the materials were 'molded'). A significant disadvantage is that it is very difficult to remove the discontinuous phase from these large continuous objects. Furthermore, this product morphology is only useful for certain

- 2 -

applications. The materials can be reduced to particles by grinding, but this is expensive and leads to particles with irregular shapes and sizes.

The direct formation of HIPE polymers in the form of microbeads was disclosed in U.S. Pat. No. 5,583,162 and WO95/33553. The disclosed HIPE microbeads are produced by polymerization of a suspension of HIPE droplets.

The direct polymerization of hydrophilic monomers in an "oil-in-water-in-oil" emulsion is described in U.S. Pat. No. 4,742,086. The emulsions comprise of less than 70% internal oil phase, and are therefore not HIPE microbeads.

U.S. Pat. Nos. 5,653,992; 5,760,097; 5,863,957; 6,048,908; 6,100,306 and 6,218,440 disclose the direct synthesis of HIPE microbeads by polymerization of suspensions of HIPE droplets. The materials disclosed are either hydrophobic or hydrophilic in nature. In general, W/O HIPEs comprising substantially oil-soluble monomers lead to hydrophobic HIPE microbeads, while oil-in-water (O/W) HIPEs comprising substantially water-soluble monomers lead to hydrophilic HIPE microbeads.

A general disadvantage associated with the direct suspension polymerization of HIPE droplets is that particles are produced with a relatively broad size range. The rather broad distribution of particle sizes and shapes produced by conventional suspension polymerization is well known in the prior art (H. G. Yuan, *et al.*, *J. Macromol. Sci., Rev. Macromol. Chem. Phys.* 1991, C31, 215; R. Arshady, *Colloid Polym. Sci.* 1992, 270, 717; E. Vivaldo-Lima, *et al.*, *Ind. Eng. Chem. Res.* 1997, 36, 939). For example, U.S. Pat. No. 5,583,162 discloses that approximately 10% of the microbeads were disclosed to be "substantially spherical or substantially ellipsoid or a combination of the two".

One method for producing spherical polymer beads with much greater control over bead

- 3 -

size is sedimentation polymerization (E. Ruckenstein, *et al.*, *Polymer* 1995, 36, 2857; E. Ruckenstein, *et al.*, *J. Appl. Polym. Sci.* 1996, 61, 1949). In this process, monomer droplets are partially polymerized during sedimentation through an immiscible sedimentation medium. The size distribution of the beads so produced may be very narrow because the droplets are spatially isolated from one another during sedimentation. As such, droplet collision and exchange does not occur. U.S. Pat. No. 6,277,932 discloses a reverse phase bead polymerization process that resulted in good control over bead size products, although no materials were disclosed with a porous HIPE structure.

It is an object of the present invention, to provide a porous polymer material and a method of production thereof, where a large majority, for example 80% or more, or even up to about 100% of the material is in the form of substantially spherical beads with narrow bead size distributions. These polymeric beads have a porous structure, characterized by cavities joined by interconnecting pores (a HIPE structure), some of which are connected to the surface of the bead.

The present invention overcomes or alleviates the problems associated with current methods of producing porous polymer beads which result in beads of irregular shapes and sizes being produced.

In accordance with the first aspect of the present invention, there are provided porous crosslinked hydrophilic polymeric beads comprising;

a nominal void volume of 70% or greater;

an average diameter range of from about 0.25 mm to about 5 mm;

a standard deviation from the average diameter within the range of from about 0.1% to about 50%.

- 4 -

It is preferred that from about 50% to about 100% of the beads are substantially spherical, in addition to having a total pore volume of from about 1 ml/g to about 5 ml/g.

In a preferred embodiment, the average bead diameter of the hydrophilic beads ranges from about 0.25 mm to about 5 mm. More preferably the average bead diameter ranges from about 0.4 mm to about 3 mm and even more preferably from about 0.5 mm to about 2.5 mm.

The hydrophilic beads of the present invention possess many of the desirable properties of prior art HIPE polymers. Specifically, the hydrophilic beads are characterized by having a low density and a highly porous structure with cavities that are highly interconnected by a network of pores. The nominal void volume in the hydrophilic beads is at least about 70%, preferably in the range 75%-99%, and more preferably in the range 80%-95%. It will be apparent that the bead morphology is suitable for use in a number of applications such as packed column chromatography, catalyst supports, controlled release of active pharmaceuticals or other active ingredients, cell immobilization, and rapid fluid absorption.

The bead size distribution is relatively narrow with the standard deviation in the average bead diameter ranging from about 0.1% to about 50%. In a preferred embodiment of this invention, the standard deviation in the average bead diameter ranges from about 0.5% to about 20%. In a most preferred embodiment of this invention, the standard deviation in the average bead diameter ranges from about 1% to about 10%.

Preferably, in accordance with the present invention, about 50% to about 100% of the beads are substantially spherical. In a further preferred embodiment of the present invention, about 80% to about 100% of the beads are substantially spherical. In the most preferred embodiment of the present invention, about 95% to about 100% of the beads are substantially spherical.

- 5 -

The porous crosslinked hydrophilic polymeric beads described above have a total pore volume of from about 1ml/g to about 5ml/g, more preferably from about 1.5 ml/g to about 3 ml/g, still more preferably from about 1.8 ml/g to about 2.8 ml/g.

Also in accordance with the present invention, there is provided a method for producing porous crosslinked hydrophilic polymeric beads comprising;

forming an HIPE;

displacing the HIPE into a sedimentation medium which is substantially immiscible with the HIPE in discrete, uniformly-sized droplets;

allowing the HIPE droplets to sediment in the sedimentation medium;

at least partially polymerizing the droplets during sedimentation;

and if necessary completing the polymerization of the droplets after sedimentation, to form porous crosslinked hydrophilic beads.

The HIPE may be an O/W HIPE, in which case the aqueous continuous phase preferably comprises a substantially water-soluble hydrophilic monomer. The monomer may be self cross-linking. Alternatively, or as well, the aqueous continuous phase may comprise a substantially water-soluble crosslinker. The aqueous continuous phase may additionally comprise a polymerization initiator, and/or an emulsifier that will facilitate the formation of a stable O/W HIPE. The sedimentation medium in this case is preferably non-aqueous.

Preferably, the droplets are only partially polymerized during sedimentation. However, if so, polymerization should proceed during sedimentation to an extent sufficient to prevent coalescence of the droplets in the sedimentation medium towards or at the end of sedimentation.

The method for producing the porous crosslinked hydrophilic polymeric beads may be continuous or completed in batches, or indeed performed in a step-by-step process.

- 6 -

It will be apparent to those skilled in the art, that displacing the emulsion as discrete, uniformly sized droplets into a sedimentation medium and subsequent polymerization during sedimentation, leads to beaded materials that possess an internal porous structure that is a skeletal replica of the original HIPE, both in relation to the microscopic HIPE structure and the macroscopic structure of the HIPE droplet templates. The bead morphology allows easy removal of the internal, discontinuous oil phase. One such method of displacing the emulsion into a sedimentation medium is by injection. It will also be apparent to those skilled in the art that the average diameter of the hydrophilic bead can be controlled by variation of experimental factors such as the diameter of the injection nozzle, the injection rate, and the viscosity of the HIPE.

In a preferred process according to the invention, the aqueous continuous phase includes a monomer, a crosslinker, an initiator and an emulsifier. The non-aqueous discontinuous phase may comprise light mineral oil and the sedimentation medium may comprise a 10:1 v/v mixture of vegetable oil and light mineral oil.

The monomer can be selected from a wide range of substantially water-soluble monofunctional vinyl monomers or mixtures of two or more thereof. Suitable vinyl monomers include, for example, acrylamide; acrylic acid; sodium acrylate; methacrylic acid; hydroxyethyl acrylate; hydroxyethyl methacrylate; sodium styrene sulfonate; vinyl pyridines; vinyl pyrrolidones; *N*-methylmethacrylamide; *N*-acryloylmorpholine; and *N*-vinyl-*N*-methacetamide. The monomer component is preferably present in the continuous phase in an amount of from about 1% to about 80% by weight. The amount of the monomer component is more preferably from about 10% to about 50% by weight, most preferably from about 20% to about 40% by weight.

The crosslinker can be selected from a wide range of substantially water-soluble

- 7 -

polyfunctional vinyl monomers or mixtures of two or more thereof. Suitable crosslinkers include, for example, *N,N'*-methylene bisacrylamide; *N,N'*-diallyl acrylamide; diallylamine; diallyl methacrylamide; diallyl phthalate; diallyl malate; diallyl phosphate; divinyl sulfone; diethylene glycol divinyl ether; ethylene glycol triacrylate; and ethylene glycol tetraacrylate. Crosslinkers of this type can be used singly or as mixtures. The crosslinker component is preferably present in the continuous phase an amount of from about 0.5% to about 20% by weight. The amount of the crosslinker component is more preferably from about 1% to about 15% by weight, most preferably from about 5% to about 10% by weight.

The initiator can be selected from a wide range of substantially water-soluble free-radical initiators or mixtures of the two thereof. Suitable initiators include, for example, ammonium, sodium, or potassium persulphate; sodium peracetate; and sodium percarbonate. The initiator component is present in the continuous phase in an amount of from about 0.1% to about 5% by total weight of polymerizable monomer. The amount of the initiator component is more preferably from about 0.5% to about 4% by total weight of polymerizable monomer, most preferably from about 1% to about 2.5% by total weight of polymerizable monomer. Optionally, a redox initiation promoter may also be added (for example, *N,N,N,N*-tetramethylethyldiamine) either in the aqueous phase, the internal droplet phase, or in the sedimentation medium.

The emulsifier can be any nonionic, cationic, anionic, or amphoteric emulsifier, or mixture of two or more thereof, effective to promote the formation of a stable O/W HIPE. In one embodiment of the present invention, a mixture of sodium dodecyl sulphate and polyvinylalcohol constitutes the emulsifier. In another embodiment of the present invention, a mixture of Triton 405 and polyvinylalcohol constitutes the emulsifier. The emulsifier component is present in the continuous phase in an amount of from about 1% to about 60% by weight. The amount of the

- 8 -

emulsifier component is more preferably from about 2% to about 40% by weight, most preferably about 5% to about 25% by weight.

The oil discontinuous phase can be any substantially water-immiscible fluid that has a boiling point that is significantly higher than the polymerization temperature. Suitable oil phases include, for example, vegetable oil; light mineral oil; silicone oil; fluorocarbon oils; and higher alkanes and mixtures of two or more thereof. The boiling point of the oil phase is greater than about 50 °C, more preferably greater than about 70 °C, most preferably greater than about 90 °C.

The hydrophilic beads of the present invention are prepared from a HIPE, which comprises an emulsion of an aqueous continuous phase (in which is dissolved monomer, crosslinker, and initiator) and an oil discontinuous phase. The ratio of the two phases greatly affects the degree of porosity in the hydrophilic bead and also the pore connectivity (*i.e.*, the degree of openness in the pore structure). In the present invention, it is preferable that the percentage of oil discontinuous phase is in the range of from about 60% to about 96%, more preferably from about 75% to about 92%, most preferably from about 80% to 90%.

After forming the HIPE, the HIPE is injected into a heated sedimentation medium in the form of discrete, uniformly sized droplets. It is an aspect of the present invention that the boiling point of the oil phase is greater than about 50 °C, more preferably greater than about 70 °C, most preferably greater than about 90 °C. The rate of sedimentation of the HIPE droplets will be determined in part by the viscosity of the sedimentation medium and the difference between the density of the sedimentation medium and the average density of the HIPE droplets. If necessary, the sedimentation rate can be decreased by addition of a high molecular weight linear polymer that is miscible with the sedimentation medium (*i.e.*, by increasing the viscosity). This viscosity modifier can be any substantially water-insoluble natural or synthetic polymer that is miscible

- 9 -

with the sedimentation medium. Alternatively, the sedimentation rate can be reduced by introducing a counter-flow in the sedimentation medium in the upward direction (*i.e.*, against the direction of droplet sedimentation). Alternatively, a mixed sedimentation medium can be used to achieve the desired density and to precisely control the sedimentation velocity.

The HIPE can be prepared by utilising any of the methods outlined in the prior art, for example, forming the HIPE by slowly adding the discontinuous phase to the continuous phase while subjecting the mixture to efficient shear agitation. In one embodiment of the present invention, the HIPE is prepared using a type Rwl 1 Basic IKA paddle stirrer.

In one process according to the present invention, the HIPE is injected into a vertically-mounted sedimentation column containing a volume of a heated sedimentation medium. This can be done by simple hand injection using a syringe. In a preferred embodiment of the invention, the HIPE is injected continuously through a 0.6 mm x 25 mm nozzle at a constant rate of 0.5 ml/min using a A-99 FZ Razel syringe pump. The droplet size can be varied by varying the nozzle diameter, the HIPE viscosity, and the injection rate. In one example, the sedimentation medium was heated to 90 °C, the height of the sedimentation column was 53 cm, and the time taken for droplet sedimentation was approximately 5-20 seconds.

Partial polymerization of the HIPE droplets occurs during sedimentation. Upon arriving at the bottom of the sedimentation column, the droplets are sufficiently rigid to prevent agglomeration between droplets. Thus, no stabilizers are required in the sedimentation medium to inhibit droplet coalescence. Polymerization is completed to form hydrophilic beads by heating the partially polymerized droplets in the sedimentation medium or after recovery therefrom. In a preferred embodiment where the monomer is acrylamide, the crosslinker is *N,N'*-methylene bisacrylamide, the free radical initiator is ammonium persulphate and the droplets are heated at

- 10 -

90 °C for a period of 2 h.

The polymerization stage converts the HIPE droplets into solid beads. The beads can be recovered by decanting the sedimentation medium. Typically, the sedimentation medium can be reused in subsequent polymerizations. The beads are washed with a solvent that is suitable to remove traces of the sedimentation medium plus any unreacted monomer.

For example the hydrophilic beads can be washed in acetone. In one example, the hydrophilic bead product was washed ten times with acetone. The discontinuous oil phase can be removed by washing with any suitable solvent. In one further example, the discontinuous oil phase was removed from the hydrophilic bead product by continuous extraction using supercritical carbon dioxide (200 bar, 35 °C). In a preferred embodiment, the discontinuous oil phase was removed by Soxhlet extraction using cyclohexane (15 h). Residual washing solvent and any residual water are removed by drying under vacuum.

The porous hydrophilic beads according to the present invention and the process of the invention, will now be more particularly described, by way of example only, with reference to the accompanying examples and drawings

Figure 1a is an optical microscope image of example 1.

Figure 1b is an optical microscope image of example 2.

Figure 1c is an optical microscope image of example 4.

Figure 1d is an optical microscope image of example 5.

Figure 2 illustrates an electron micrograph of the internal structure of one bead in example 1.

Figure 3 illustrates an electron micrograph of the bead surface of example 7.

Figure 4 illustrates an electron micrograph of the bead surface of example 8.

Figure 5 illustrates an electron micrograph of internal structure of the bead in example 8.

Figure 6 is an optical image of the beads produced in example 6.

Figure 7 is an optical image of the beads produced in example 7.

Figure 8 is an optical image of the beads produced in example 8.

Example 1

Hydrophilic HIPE beads were prepared by continuous sedimentation polymerisation of a HIPE comprising an aqueous continuous phase (containing the monomer) and an oil discontinuous phase. The components and amounts used in this study are indicated in Table 1 below. The components of the hydrophilic monomer phase were mixed in a beaker by stirring at room temperature. After adding the surfactant (sodium dodecyl sulphate) and the co-surfactant (polyvinylalcohol, MW = 9,000-10,000 g/mol, 80% hydrolysed), the initiator (ammonium persulphate) was added. The aqueous monomer phase was stirred mechanically while slowly adding light mineral oil to form a HIPE.

A glass sedimentation column (53 cm in length, outside diameter 5.6 cm, internal diameter 4.6 cm) was used. Light mineral oil and vegetable oil (1:10 v/v) was added and this mixed oil was used as the sedimentation medium. The level of the oil was 5 cm from the top of the glass column. The sedimentation medium was heated to 90 °C. The HIPE was injected using a A-99 FZ Razel syringe pump through a 0.6 mm x 25 mm needle at a flow rate of 0.5 ml/min.

After the injection of the HIPE, the partially gelled beads were collected at the bottom of the sedimentation column. Complete polymerization of the beads was achieved by heating the column for 2.5 h at 90 °C.

The collected beads were washed ten times with acetone and allowed to dry in air at room

- 12 -

temperature. The internal oil phase was removed by Soxhlet extraction with cyclohexane for 15 h. The beads were then dried overnight in a vacuum oven at 50 °C.

The beads have a skeletal density very similar to that of the equivalent non-porous cross-linked polymer, which suggests that the pores are interconnected and that there is little closed porosity.

Figure 1 shows an optical microscope image of a range of beads relating to examples 1, 2, 4 and 5. The mean bead diameter of figure 1a is 1.56 mm and the standard deviation in bead diameter is 8.2 %. The mean bead diameter of figure 1b is 1.61 mm and the standard deviation in bead diameter is 6.96%. The total pore volume in figure 1b is 2.14 ml/g. The mean bead diameter of figure 1c is 1.20 mm and the standard deviation in bead diameter is 12.60%. The mean bead diameter of figure 1d is 1.63 mm and a standard deviation in bead diameter is 10.75%

Figure 2 shows an electron micrograph of a fractured bead, showing the internal structure of the bead of example 1 (x2000 magnification). The BET surface area of the beads was 5.98 ml/g. The total pore volume (or intrusion volume) as measured by mercury intrusion porosimetry was 2.51 ml/g.

Figure 3 illustrates an electron micrograph of the bead surface of example 7. Figure 7 is an optical microscope image of example 7, beads of which has a mean bead diameter of 2.19 mm and a standard deviation in bead diameter of 12.23%.

Figure 4 illustrates an electron micrograph of the bead surface of example 8, Figure 5 shows the internal structure of the bead in example 8 and Figure 8 is an optical microscope image of example 8 which has a mean bead diameter of 2.24 mm and a standard deviation in bead diameter of 11.95 %.

Figure 6 is an optical microscope image of example 6, which has a mean bead diameter

- 13 -

of 1.51mm and a standard deviation in bead diameter of 8.86%.

Figure 7 is an optical microscope image of example 7, beads of which had a mean bead diameter of 2.19 mm and a standard deviation in bead diameter of 12.23%

Table 1: HIPE Components for Example 1

(1) Aqueous monomer/crosslinker solution

Acrylamide:	15.36 g
<i>N,N'</i> -methylene bisacrylamide:	3.11 g
Deionized water:	40 ml

(2) 1.5 ml of the above solution was emulsified with:

Sodium dodecyl sulphate:	0.60 g
Polyvinylalcohol, MW = 9,000-10,000:	0.06 g
Ammonium persulphate:	0.025 g
Light mineral oil:	6.0 ml

(3) Sedimentation Medium:

Vegetable oil:	770 ml
Light mineral oil:	70 ml
Temperature:	90 °C

Examples 2-8

Exemplary preferred HIPE beads were prepared according to the following general protocol. The details of specific examples are set forth in Table 2-8.

1. An aqueous hydrophilic monomer solution was prepared.

- 14 -

2. The surfactant, co-surfactant, and initiator were added step-wise, with stirring.
3. The discontinuous oil phase was added with mechanical stirring to form a HIPE.
4. The emulsion was injected into the heated oil sedimentation medium as discrete, uniformly sized droplets.
5. After partial gelation during sedimentation, the beads were collected at the bottom of the sedimentation column. Polymerization was completed over a period of 2.5 h at 90 °C.
6. The beads were separated from the sedimentation medium by decanting and washed 10 times with acetone. The internal oil phase was extracted from the beads using cyclohexane in a Soxhlet extractor for approximately 15 h.
7. The beads were dried in a vacuum oven at 50 °C overnight.

Table 2: HIPE Components for Example 2**(1) Aqueous monomer/crosslinker solution**

Acrylamide:	15.36 g
<i>N,N'</i> -methylene bisacrylamide:	3.11 g
Deionized water:	40 ml

(2) 1.5 ml of the above solution was emulsified with:

Sodium dodecyl sulphate:	0.60 g
Polyvinylalcohol, MW = 9,000-10,000:	0.03 g
Ammonium persulphate:	0.025 g
Light mineral oil:	6.0 ml

(3) Sedimentation Medium:

Vegetable oil:	770 ml
Light mineral oil:	70 ml

- 15 -

Temperature: 90 °C

Mean bead diameter = 1.61 mm. Standard deviation in bead diameter = 6.96%. Total pore volume (intrusion volume) = 2.14 ml/g.

Table 3: HIPE Components for Example 3**(1) Aqueous monomer/crosslinker solution**

Acrylamide:	15.36 g
<i>N,N'</i> -methylene bisacrylamide:	3.11 g
Deionized water:	40 ml

(2) 1.5 ml of the above solution was emulsified with:

Sodium dodecyl sulphate:	0.20 g
Polyvinylalcohol, MW = 9,000-10,000:	0.08 g
Ammonium persulphate:	0.025 g
Light mineral oil:	8.5 ml

(3) Sedimentation Medium:

Vegetable oil:	770 ml
Light Mineral oil:	70 ml
Temperature:	90 °C

Mean bead diameter = 1.53 mm. Standard deviation in bead diameter = 23.03%. Total pore volume (intrusion volume) = 2.65 ml/g.

Table 4: HIPE Components for Example 4

- 16 -

(1) Aqueous monomer/crosslinker solution

Acrylamide:	15.36 g
<i>N,N'</i> -methylene bisacrylamide:	3.11 g
Deionized water:	40 ml

(2) 1.5 ml of the above solution was emulsified with:

Sodium dodecyl sulphate:	0.25 g
Polyvinylalcohol, MW = 9,000-10,000:	0.05 g
Ammonium persulphate:	0.030 g
Light mineral oil:	8.5 ml

(3) Sedimentation Medium:

Vegetable oil:	770 ml
Light mineral oil:	70 ml
Temperature:	90 °C

Mean bead diameter = 1.20 mm. Standard deviation in bead diameter = 12.60%.

Table 5: HIPE Components for Example 5**(1) Aqueous monomer/crosslinker solution**

Acrylic Acid:	15.36 g
<i>N,N'</i> -methylene bisacrylamide:	3.10 g
Deionized water:	40 ml

(2) 1.5 ml of the above solution was emulsified with:

Sodium dodecyl sulphate:	0.40 g
Polyvinylalcohol, MW = 9,000-10,000:	0.06 g

- 17 -

Ammonium persulphate:	0.036 g
<i>N,N,N,N</i> -Tetramethylethylenediamine:	50 μ L
Light mineral oil:	6.0 ml

(3) Sedimentation Medium:

Vegetable oil:	770 ml
Light mineral oil:	70 ml
Temperature:	90 °C

Mean bead diameter = 1.63 mm. Standard deviation in bead diameter = 10.75%.

Table 6: HIPE Components for example 6**(1) Aqueous monomer/crosslinker solution:**

Acrylamide:	15.36 g
N, N'-methylene bisacrylamide:	3.11 g
Polyvinylalcohol, MW = 9,000-10,000	2.50 g
Deionized water:	40 ml

(2) 3.0 ml of the above solution was emulsified with:

Sodium dodecyl sulphate, 98%:	0.80 g
Light mineral oil:	14.0 ml
<i>N,N,N,N</i> -Tetramethylethylenediamine:	1 drop in oil

(using 0.6mm X 25mm needle)

Ammonium persulphate 10 wt % aqueous solution 0.40 ml

(3) Sedimentation medium:

Vegetable oil:	770 ml
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- 18 -

Light mineral oil: 70 ml

Temperature: 90 °C

Mean bead diameter = 1.51 mm. Standard deviation in bead diameter = 8.86 %.

Table 7: HIPE Components for example 7

(1) Aqueous monomer/crosslinker solution:

Acrylamide: 15.36 g

N, N'-methylene bisacrylamide: 3.11 g

Polyvinylalcohol, MW = 9,000-10,000 2.50 g

Deionized water: 40 ml

(2) 3.0 ml of the above solution was emulsified with:

Sodium dodecyl sulphate, 98%: 0.70 g

Light mineral oil: 12.0 ml

N,N,N,N-Tetramethylethylenediamine: 1 drop in oil

(using 0.6mm X 25mm needle)

Ammonium persulphate 10 wt % aqueous solution 0.45 ml

(3) Sedimentation medium:

Light mineral oil: 750 ml

Heavy mineral oil: 200 ml

N,N,N,N-Tetramethylethylenediamine: 23.0 ml

Temperature: 60 °C

- 19 -

Mean bead diameter = 2.19 mm. Standard deviation in bead diameter = 12.23 %.

Table 8: HIPE Components for example 8

(1) Aqueous monomer/crosslinker solution:

Acrylamide:	15.36 g
N, N'-methylene bisacrylamide:	3.11 g
Polyvinylalcohol, MW = 9,000-10,000	2.50 g
Deionized water:	40 ml

(4) 3.0 ml of the above solution was emulsified with:

Sodium dodecyl sulphate, 98%:	0.65 g
Light mineral oil:	10.50 ml
N,N,N,N-Tetramethylethylenediamine:	1 drop in oil

(using 0.6mm X 25mm needle)

Ammonium persulphate 10 wt % aqueous solution 0.45 ml

(5) Sedimentation medium:

Light mineral oil:	750 ml
Heavy mineral oil:	200 ml
N,N,N,N-Tetramethylethylenediamine:	23.0 ml
Temperature:	60 °C

Mean bead diameter = 2.24 mm. Standard deviation in bead diameter = 11.95 %.

- 20 -

CLAIMS

1. Porous crosslinked hydrophilic polymeric beads comprising;
a nominal void volume of 70% or greater;
an average diameter range of from 0.25 mm to 5 mm;
a standard deviation from the average diameter within the range of from 0.1% to 50%.
2. A porous crosslinked hydrophilic polymeric bead described in claim 1 wherein from 50% to 100% of the beads are substantially spherical.
3. A porous crosslinked hydrophilic polymeric bead described in claim 1 and claim 2, wherein the total pore volume range from 1 ml/g to 5 ml/g.
4. A method for producing porous crosslinked hydrophilic polymeric beads comprising;
forming an HIPE;
displacing the HIPE into a sedimentation medium which is substantially immiscible with the HIPE in discrete, uniformly-sized droplets;
allowing the HIPE droplets to sediment in the sedimentation medium;
at least partially polymerizing the droplets during sedimentation;
and if necessary completing the polymerization of the droplets after sedimentation, to form porous crosslinked hydrophilic beads.
5. A method for producing porous crosslinked hydrophilic polymeric beads according to claim 4, wherein the process is continuous.

- 21 -

6. A method for producing porous crosslinked hydrophilic polymeric beads according to claim 5, wherein the monomer is selected from one the following group of vinyl monomers or is a mixture of two or more thereof; acrylamide; acrylic acid; sodium acrylate; methacrylic acid; hydroxyethyl acrylate; hydroxyethyl methacrylate; sodium styrene sulfonate; vinyl pyridines; vinyl pyrrolidones; *N*-methylmethacrylamide; *N*-acryloylmorpholine; and *N*-vinyl-*N*-methacetamide.

7. A method for producing porous crosslinked hydrophilic polymeric beads as claimed in claims 4 to 6, wherein the monomer component is present in the continuous phase in an amount ranging from 1% to 80% by weight.

8. A method for producing porous crosslinked hydrophilic polymeric beads as claimed in claims 4 to 7, wherein the crosslinker is selected from one of the following group of crosslinkers or is a mixture of two or more thereof;

N,N'-methylene bisacrylamide; *N,N'*-diallyl acrylamide; diallylamine; diallyl methacrylamide; diallyl phthalate; diallyl malate; diallyl phosphate; divinyl sulfone; diethylene glycol divinyl ether; ethylene glycol triacrylate; and ethylene glycol tetraacrylate.

9. A method for producing porous crosslinked hydrophilic polymeric beads as claimed in claims 4 to 8, wherein the crosslinkers component is present in the continuous phase in an amount ranging from 0.5% to 20% by weight.

10. A method for producing porous crosslinked hydrophilic polymeric beads as claimed in

- 22 -

claims 4 to 9, wherein the initiator can be selected from one of the following group of initiators or is a mixture of two or more thereof; ammonium; sodium; or potassium persulphate; sodium peracetate; and sodium percarbonate.

11. A method for producing porous crosslinked hydrophilic polymeric beads as claimed in claims 4 to 10, wherein the initiator component is present in the continuous phase in an amount ranging from 0.1% to 5% by total weight of polymerizable monomer.

12. A method for producing porous crosslinked hydrophilic polymeric beads as claimed in claims 4 to 11, wherein the emulsifier can be selected from one of the following groups of emulsifiers or is a mixture of two or more thereof;
nonionic; cationic; anionic; and amphoteric.

13. A method for producing porous crosslinked hydrophilic polymeric beads as claimed in claims 4 to 12, wherein the emulsifier component is present in the continuous phase in an amount ranging from 1% to 60% by weight.

14. A method for producing porous crosslinked hydrophilic polymeric beads as claimed in claims 4 to 13, wherein the oil discontinuous phase comprise any substantially water-immiscible fluids selected from one of the following group or is a mixture of two or more thereof;
vegetable oil; light mineral oil; silicone oil; fluorocarbon oils; and higher alkanes.

15. A method for producing porous crosslinked hydrophilic polymeric beads as claimed in

- 23 -

claims 4 to 14, wherein the percentage of oil in the discontinuous phase is in an amount ranging from 60% to 96%.

16. A method for producing porous crosslinked hydrophilic polymeric beads as claimed in claims 4 to 15, wherein the sedimentation rate is decreased by addition of a high molecular weight linear polymer that is miscible with the sedimentation medium.

17. A method for producing porous crosslinked hydrophilic polymeric beads as claimed in claims 4 to 16, wherein the beads are washed in acetone.

18. A method for producing porous crosslinked hydrophilic polymeric beads as claimed in claims 4 to 17, wherein the discontinuous oil phase is removed from the hydrophilic polymeric beads by continuous supercritical carbon dioxide extraction.

19. A method for producing porous crosslinked hydrophilic polymeric beads as claimed in claims 4 to 17, wherein the discontinuous oil phase is removed from the hydrophilic polymeric beads by Soxhlet extraction using cyclohexane.

20. A porous crosslinked hydrophilic polymeric bead and method of production as substantially as herein described with reference to and as illustrated in the accompanying examples and drawings.

1/4

Figure 1

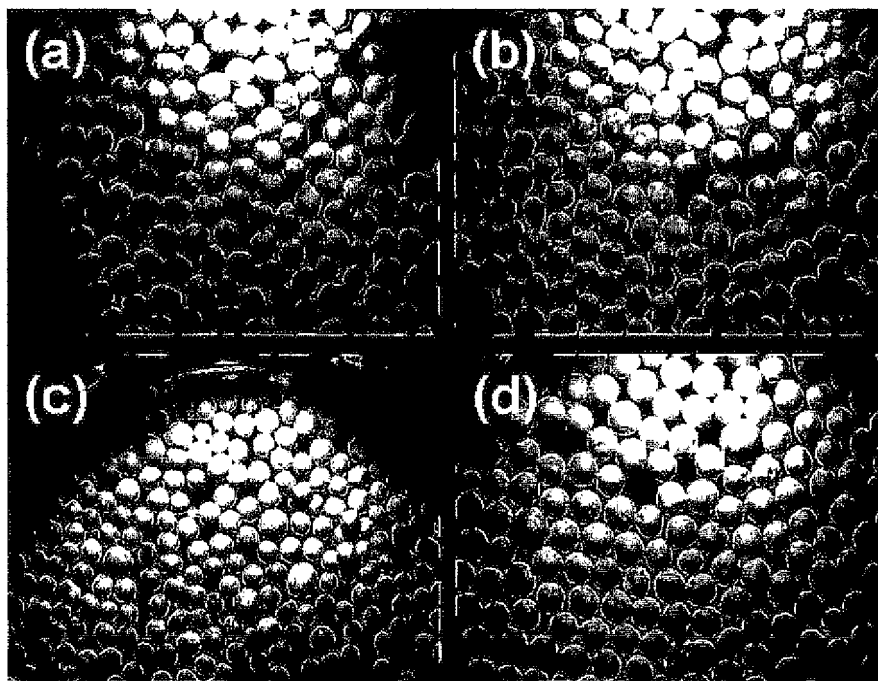
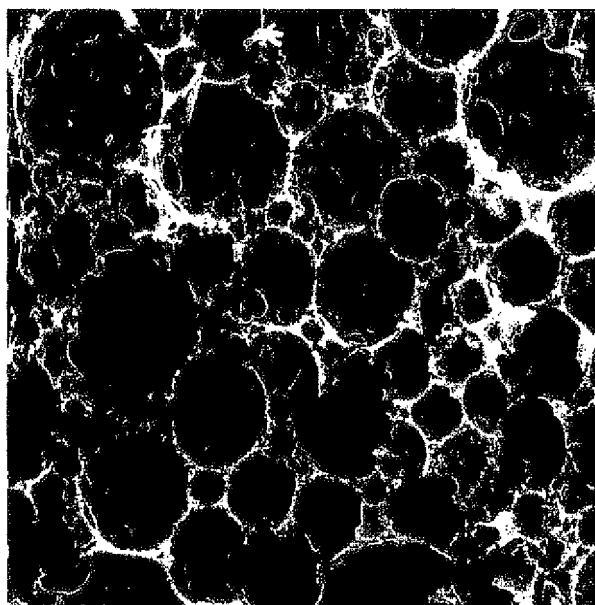


Figure 2



2/4

Figure 3

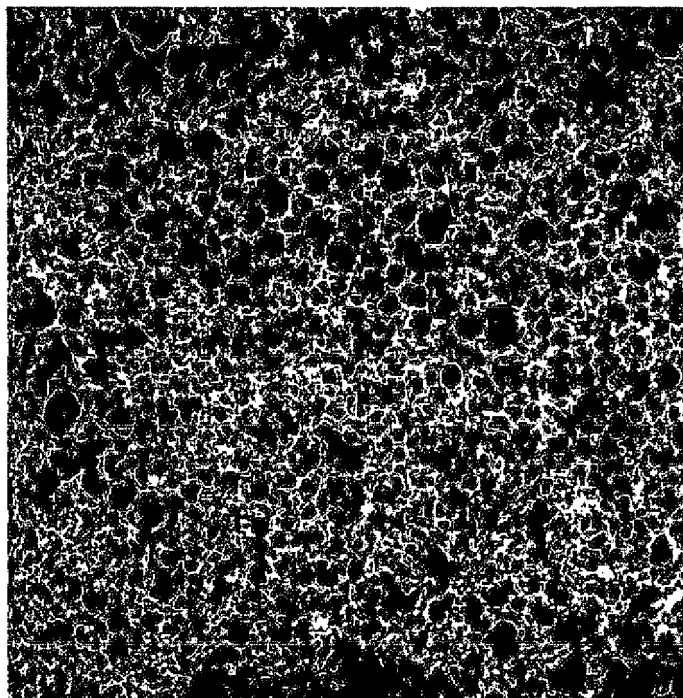
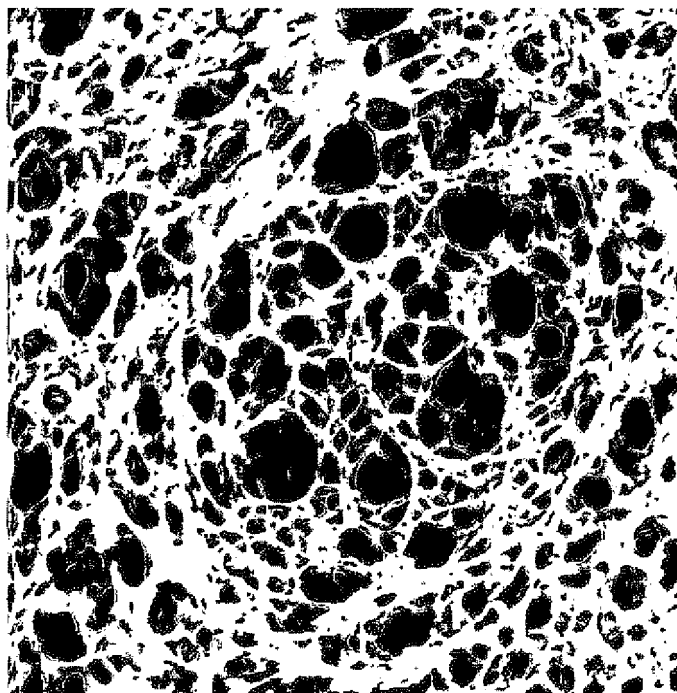


Figure 4



3/4

Figure 5

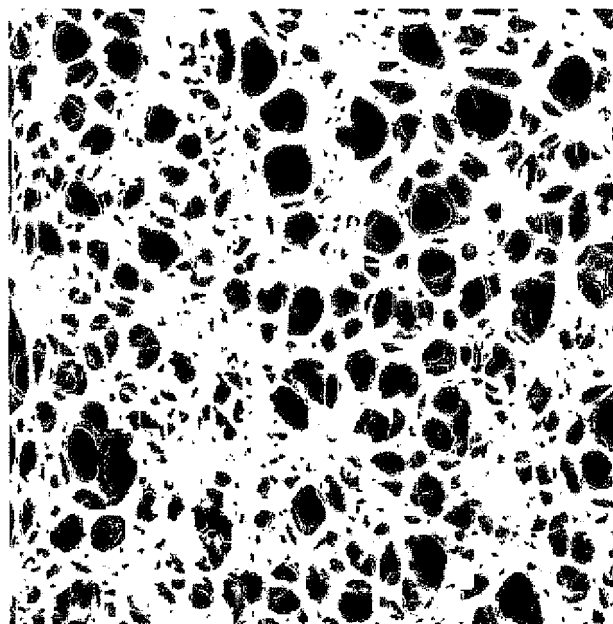
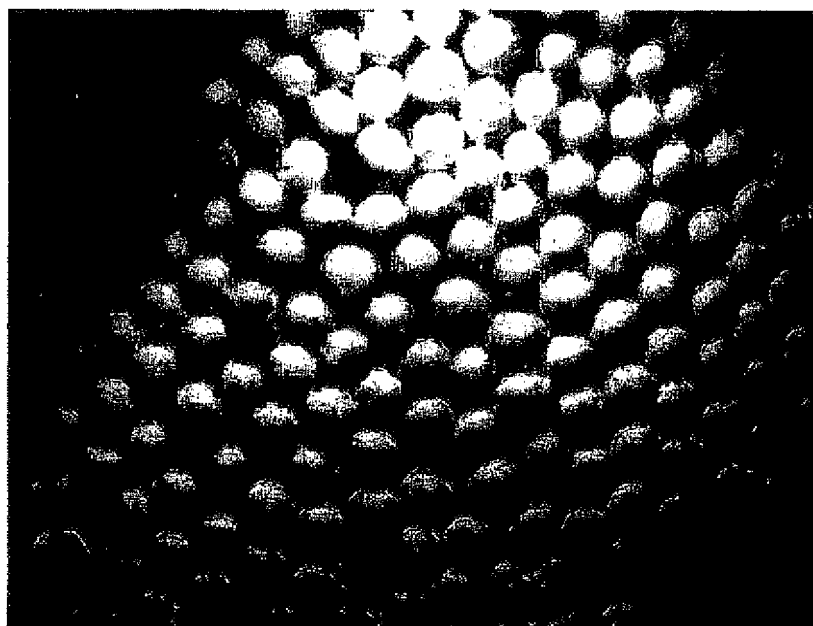


Figure 6



4/4

Figure 7

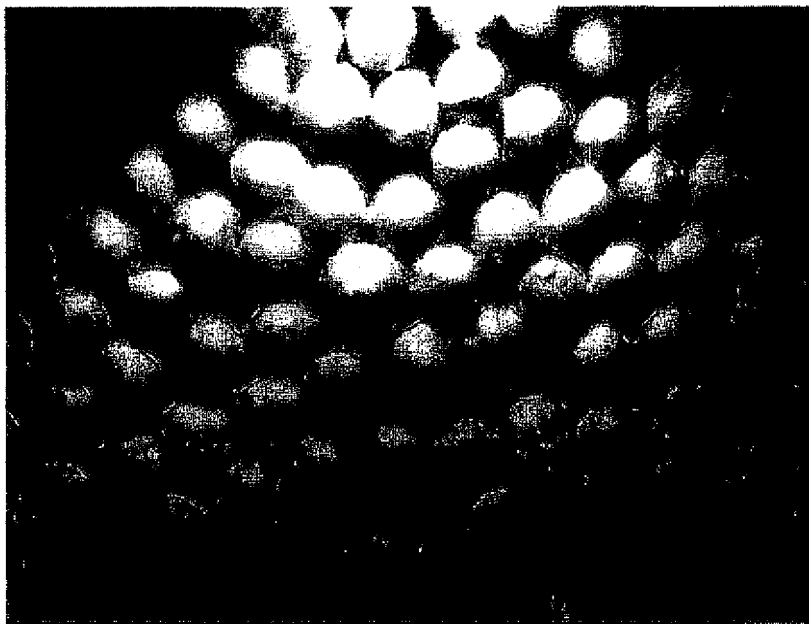
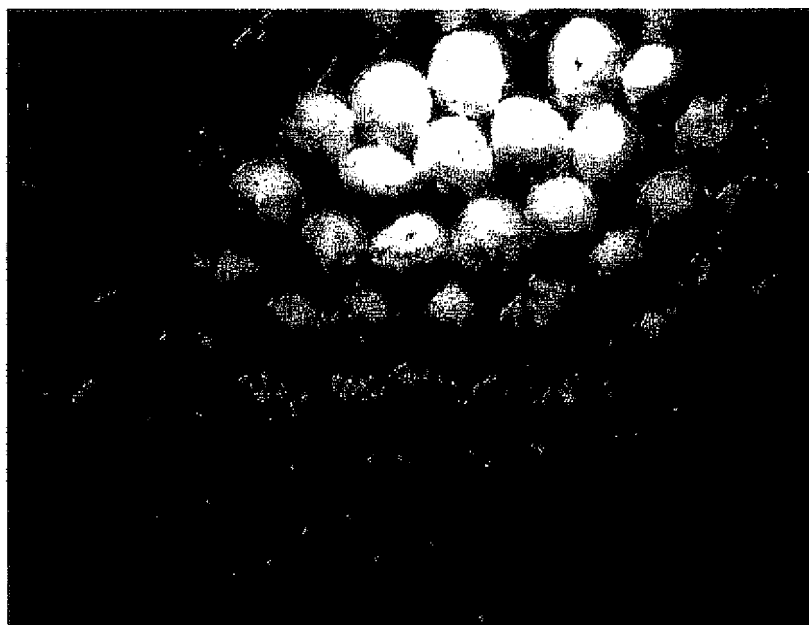


Figure 8



INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/GB 03/01760

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C08J9/28 C08F2/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C08F C08J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, COMPENDEX, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	RUCKENSTEIN E ET AL: "Sedimentation polymerization" POLYMER, ELSEVIER SCIENCE PUBLISHERS B.V, GB, vol. 36, no. 14, 1995, pages 2857-2860, XP004025717 ISSN: 0032-3861 cited in the application the whole document	1-20
A	US 5 863 957 A (LI NAI-HONG ET AL) 26 January 1999 (1999-01-26) cited in the application claims 1,2; tables 2,4	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

25 July 2003

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

Internal	Application No
PCT/GB	03/01760

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5863957 A	26-01-1999	US 5760097 A	02-06-1998
		US 5653922 A	05-08-1997
		US 5583162 A	10-12-1996
		US 6100306 A	08-08-2000
		AU 702241 B2	18-02-1999
		AU 2693795 A	04-01-1996
		AU 7618698 A	15-10-1998
		CA 2190731 A1	14-12-1995
		CN 1150764 A	28-05-1997
		EP 0764047 A1	26-03-1997
		JP 10501173 T	03-02-1998
		WO 9533553 A1	14-12-1995
